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Title:

Treatment with rituximab in patients with polyneuropathy with anti-MAG antibodies.

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Ethic committee of CHU de Nice approval was obtained and the patient gave informed consent.

Abstract

We report on a series of six patients diagnosed as anti-MAG polyneuropathy treated with rituximab. Nine months after the infusion of rituximab, sensory deficiency considered through the INCAT sensory score was improved in 5 patients and functional disability quantified by the overall neuropathy limitation scale was improved in 3 patients. Titers of anti-MAG antibodies and of monoclonal IgM gammopathy decreased respectively by 43% and 31%. No serious adverse event was observed. We did not find any predictive factors statistically related with the response to treatment.

Keywords

Rituximab, polyneuropathy with anti-MAG antibodies

Efficacy of rituximab (RTX), a monoclonal anti-CD20 antibody, has been suggested in a recent controlled trial in polyneuropathies with antibodies against myelin-associated glycoprotein (PN-MAG) [1]. Aims of this study were to evaluate the efficacy and safety of RTX in PN-MAG and to search for predictive factors of response to treatment.

Methods:

Six patients fulfilling diagnosis criteria for PN-MAG [2] received 4 weekly infusions of RTX (375 mg/m²). Clinical status of each patient was evaluated, before treatment (M0) then every 3 months during 9 months, by assessing Overall Neuropathy Limitation Scale (ONLS) [3], INCAT Sensory Score (ISS) [4], and MRC sumscore on 28 muscle groups [5]. Anti-MAG titers (Buhlmann ELISA technique) and B cells expressing CD19 blood count were concomitantly quantified. Nerve conduction studies were performed before treatment and 9 months after, on fibular, tibial, median and ulnar nerves [5]. Treatment was considered efficient only when ONLS score decreased by at least 1 point at M9. Demographic, clinical, biological and electrophysiological status before RTX, were statistically compared between patients with efficient and non-efficient response to treatment using the Mann-Whitney and Fisher's exact tests. The level of statistical significance was set at $p=0.05$. Patients were asked to give informed consent for use of data in a journal publication.

Results:

Mean age of patients (70 yo, range 57-86), duration before treatment from onset of the disease (5 years, range 2-10), main clinical manifestations of each patient and previous immunotherapies are detailed in table 1. Before RTX treatment, ONLS score ranged from 2 to 6 (mean 3.7) and ISS score from 2 to 12 (mean 6.2). Nine months after the last RTX infusion, ONLS score improved by 1 point in 2 patients, by 2 points in 1, remained stable in the 3 others. ISS score improved in 5 patients (mean 3.8 points), MRC score improved in 3 patients

(mean 2.7 points). Decrease of anti-MAG titers was observed in all the 6 patients at M9 by a mean of 43% (figure 1). By the meantime, IgM monoclonal titers decreased in 5 patients but did not change in one. As expected, CD19 B cells blood count dramatically decreased, after treatment and stayed low at M9 ($138 \times 10^9/l$ at M0 vs $2.5 \times 10^9/l$ at M3 vs $40 \times 10^9/l$ at M9). RTX treatment did not modify the mean CD4 and CD8 lymphocytes blood counts (respectively $674 \times 10^9/l$ at M0 vs $789 \times 10^9/l$ at M9; and $448 \times 10^9/l$ at M0 vs $416 \times 10^9/l$ at M9) as the mean gammaglobulins titers ($9.7g/l$ at M0 vs $9g/l$ at M9). No change in individual or overall electrophysiological data was evidenced when comparing examination before treatment and 9 months after treatment. No serious adverse event was reported.

Demographic, clinical, biological and electrophysiological data at baseline, including MAG titers and IgM monoclonal titers, were not statistically different in the 3 patients who improved their ONLS score at M9 compared to the 3 patients who did not.

Discussion:

Experimental pathogenicity of anti-MAG antibodies has been established in anti-MAG polyneuropathies [6]. RTX is a monoclonal antibody designed to target the B-cells producing anti-MAG antibodies and then expected to reverse the pathogenic process.

In clinical practice, therapeutic benefits of RTX are known to be delayed and are reported to be more evident on sensory deficiency than on functional disability. Our results confirm those of previous studies: improvement of sensory deficiency in half to 2/3 of the treated patients, improvement of the functional disability in less than half of the treated patients, decrease of IgM monoclonal component and of anti-MAG titers respectively by 30 to 74% and by 44 to 87%, as assessed 8 or 12 months after the RTX infusions [1, 7, 8, 9, 10].

In this study, we did not find any predictive factor of response to RTX treatment, including type of the underlying hemopathy and disease duration prior to treatment. Predictive value of anti-MAG antibodies titers is not clear in the literature: RTX is more efficient when

anti-MAG antibodies titers are moderately elevated in one study [9] and when titers are high in another [1]. Better improvement was reported in patients with more severe sensory deficit at baseline [1].

Treatment with RTX improved functional disability in half of our PN-MAG population. Treatment was safe, no serious adverse event occurred during the 9 months period of follow up. As no predictive factor of efficacy appears informative, RTX should be reserved to patients impaired in their daily life. Studies in larger cohorts are needed to confirm.

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